REMARKS

Claims 2-4, 6, 8-10, and 13-36 are pending. Claims 18 and 20-32 are withdrawn. Claims 2-4, 6, 8-10, 13-17, 19, and 33-36 have been rejected. By this amendment, Claims 6, 10, 18, and 20-32 have been canceled. Claims 2-4, 8, 13, 17, 19, 33, and 34 have been amended. Claims 38-44 have been added. Reconsideration of Claims 2-4, 8, 9, 13-17, 19, and 33-36, and allowance of Claims 2-4, 8, 9, 13-17, 19, 33-36, and 38-44 is respectfully requested.

The Withdrawal of Previous Rejections

The withdrawal of the previous rejections of Claim 1-19 under 35 U.S.C. § 112, first and second paragraphs, and 35 U.S.C. § 103(a) in view of the Choi and Heller references is noted with appreciation.

The Claimed Invention: Independent Claim 33.

Claim 33 is the pending independent claim. Claims 2-4, 6, 8-10, 13-17, 19, and 34-36 depend from Claim 33, or claims that depend from Claim 33.

Claim 33 recites a composition that includes a hydrophilic conjugate. The hydrophilic conjugate has three components: (1) a hydrophobic component linked to (2) a hydrophilic component by (3) a pH-sensitive linkage. Claim 33 also recites two additional features: (a) the pH-sensitive linkage is stable at a pH between 6.8 and 8 and hydrolyzed at a pH less than 6.5 to release the hydrophobic component; and (b) the hydrophobic component is membrane-disruptive and allows enhanced transport through a membrane only when released from the hydrophilic conjugate. Therefore, at a pH less than 6.5, the conjugate's pH-sensitive linkage cleaves releasing the hydrophobic component from the hydrophilic component. When released from the hydrophilic component, the hydrophobic component becomes membrane disruptive thereby allowing for transport through the membrane. When the conjugate further includes a therapeutic or diagnostic agent, release of the hydrophobic component by pH-sensitive linkage cleavage

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allows for the released hydrophobic component, which is now membrane disruptive, to disrupt the membrane thereby allowing delivery of the therapeutic or diagnostic agent through the disrupted membrane. See FIGURES 3 and 4 of the application as filed.

The cited references, either alone or in any combination, fail to describe, suggest, or provide any motivation to make the conjugate having the three components recited in Claim 33.

The Rejection of Claims 2-4, 8-10, 14, 15, and 33-35 Under 35 U.S.C. § 102(b)

Claims 2-4, 8-10, 14, 15, and 33-35 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,258,453, issued to Kopecek et al. Withdrawal of this grounds for rejection is respectfully requested for the following reasons.

Claim 33 is the independent claim from which Claims 2-4, 8-10, 14, 15, 34, and 35 depend. As noted above, Claim 33 relates to a hydrophilic conjugate having three components: (1) a hydrophobic component, which is membrane-disruptive and allows enhanced transport through a cellular membrane only when released from the hydrophilic conjugate, linked to (2) a hydrophilic component by (3) a pH-sensitive linkage that is stable at a pH between 6.8 and 8 and hydrolyzed at a pH less than 6.5 to release the hydrophobic component.

The Kopecek reference does not describe a hydrophilic conjugate having a hydrophobic component linked to a hydrophilic component through a pH-sensitive linkage that is stable at a pH between 6.8 and 8 and hydrolyzed at a pH less than 6.5.

The Kopecek reference describes compositions for the treatment of cancerous tissues that include an anti-cancer drug and a photoactivatable drug attached to a hydrophilic copolymeric carrier. The anti-cancer drug is attached to the polymeric carrier by side chains that are stable in the blood stream, but susceptible to hydrolysis by a specific lysosomal enzyme (cathepsin B) intracellularly.

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The Examiner equates the copolymer to the hydrophilic conjugate of the claimed invention. Representative copolymers are described in Cols. 10-16 of the reference. Referring to Copolymer I, illustrated at Col. 11, the Examiner appears to have equated (1) the hydrophilic copolymer backbone with the hydrophobic component of the claimed conjugate, (2) the polypeptide side chain grafted to the polymer backbone with the hydrophilic component of the claimed conjugate, and (3) the amide bond between the grafted polypeptide side chain and the anti-cancer drug (or the amide bond between the backbone and side chain) with the pH-sensitive linkage of the claimed conjugate. In concluding that the copolymer described in the reference anticipates the claimed conjugate, the Examiner has presumed that the pH-sensitive linkage of the claimed composite, which is recited as being stable at a pH between 6.8 and 8.0 and hydrolyzed at a pH less than 6.5 to release the hydrophobic component, is inherent in the copolymer described in the Kopecek reference. Applicants respectfully disagree.

The Kopecek Polymers Lack a pH-Sensitive Linkage. The polymers described in the reference do not include a pH-sensitive linkage that is "stable at a pH between 6.8 and 8.0 and hydrolyzed at a pH less than 6.5," as in the claimed invention. The reference describes a water-soluble polymer (i.e., hydrophilic polymer) having a drug covalently coupled to the polymer through an enzyme-degradable peptide linkage. The linkage described in the reference is not sensitive to pH in the recited pH range or at physiological pHs (i.e., amide linkages are degradable only at extremely high pH or extremely low pH), but rather is sensitive to enzyme degradation. The peptide sequences used in the polymers are specifically designed to allow for degradation by a specific lysosomal enzyme (e.g., cathepsin B). Enzyme degradation occurs for the Kopecek polymers as a result of biological action that happens to occur at low pH in the lysosome, but is not induced by pH. In contrast, in the claimed invention, the pH-sensitive linkage is cleaved by a pH-induced, general, non-specific hydrolysis reaction. Furthermore, the

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Kopecek polymer's peptide (amide) linkages are not "stable at a pH between 6.8 and 8.0 and hydrolyzed at a pH less than 6.5," as in the claimed invention. Amide linkages, such as in peptides, are stable at pH less than 6.5 and are only hydrolyzed at high pH, significantly higher pH than endosomal pH (slightly acidic pH).

Because the cited reference fails to exactly describe the claimed invention, the reference is not anticipatory. Withdrawal of the rejection is respectfully requested.

The Rejection of Claims 2-4, 8-10, 14, 15, and 33-35 Under 35 U.S.C. § 102(b)/103(a)

Claims 2-4, 8-10, 14, 15, and 33-35 stand rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,258,453, issued to Kopecek et al. Withdrawal of these grounds for rejection is respectfully requested for the following reasons.

Claim 33 is the independent claim from which Claims 2-4, 8-10, 14, 15, 34, and 35 depend.

For the reasons noted above, because the cited reference fails to exactly describe the claimed invention, the reference is not anticipatory. Withdrawal of the rejection is respectfully requested.

Furthermore, applicants submit that the cited reference fails to teach, suggest, provide any motivation to make, or otherwise render obvious the claimed invention. The Kopecek polymers do not include a pH-sensitive linkage that, at pH less than 6.5, cleaves and releases a membrane-disruptive hydrophobic component thereby affecting membrane disruption and drug delivery. The Kopecek polymers include a peptide linkage that is degraded by enzymolysis in the lysosome, not by acidic pH-induced hydrolysis in the endosome. The enzymolysis releases a drug that then diffuses out of the lysosome without any membrane disruption. In contrast, hydrolysis of the pH-sensitive linkage in the claimed invention releases a membrane-disruptive

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hydrophobic component that disrupts the membrane thereby delivering the drug (when the conjugates of the invention further include a drug).

The cited reference fails to suggest the claimed invention because the cited reference fails to teach or suggest a pH-sensitive linkage. The cited reference provides for drug delivery by specific enzymatic action on the polymer. The claimed invention provides for drug delivery by simple acid hydrolysis of a chemically labile linkage that is pH-sensitive in the environment of the endosome. One skilled in the art would not be motivated by the teaching of the Kopecek reference to modify the enzyme-degradable linkage that is designed for specific for lysosomal enzymolysis to arrive at the pH-sensitive linkage of the claimed invention. The Kopecek polymer is directed to drug delivery through specific enzymatic action. The conjugate of the claimed invention is not.

Because the cited reference fails to teach, suggest, provide any motivation to make, or otherwise render obvious the claimed invention, the claimed invention is nonobvious and patentable of the cited reference. Withdrawal of the rejection is respectfully requested.

The Rejection of Claims 2-4, 8-10, 13-15, 19, and 33-36 Under 35 U.S.C. § 102(e)

Claims 2-4, 8-10, 13-15, 19, and 33-36 stand rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,210,717, issued to Choi et al. Withdrawal of this grounds for rejection is respectfully requested for the following reasons.

Claim 33 is the independent claim from which Claims 2-4, 8-10, 13-15, 19, and 34-36 depend. As noted above, Claim 33 relates to a hydrophilic conjugate having three components: (1) a hydrophobic component, which is membrane-disruptive and allows enhanced transport through a cellular membrane only when released from the hydrophilic conjugate, linked to (2) a hydrophilic component by (3) a pH-sensitive linkage that is stable at a pH between 6.8 and 8 and hydrolyzed at a pH less than 6.5 to release the hydrophobic component.

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The Examiner states that the Choi reference describes a composition for delivering a selected nucleic acid and various kinds of ligands into a targeted host cell. The Examiner believes that the composition is a copolymer transport molecule that includes a hydrophilic portion and a hydrophobic portion linked through an amide bond, which the Examiner has equated to a pH-sensitive linkage.

The Choi reference describes a composition that includes a polyester polycation copolymer that is diblock copolymer having a hydrophobic polyester block bonded to a hydrophilic polycation block by an amide linkage. See Col. 2, lines 37-40. Like the Kopecek reference discussed above, the Choi reference describes a polymer that includes an amide linkage. For the same reasons noted above in regard to the Kopecek polymer, the Choi polymer does not include "a pH-sensitive linkage that is stable at a pH between 6.8 and 8 and hydrolyzed at a pH less than 6.5," as in the claimed invention.

Because the cited reference fails to exactly describe the claimed invention, the reference is not anticipatory. Withdrawal of the rejection is respectfully requested.

The Rejection of Claims 2-4, 8-10, 13-15, 19, and 33-36 Under 35 U.S.C. § 102(e)/103(a)

Claims 2-4, 8-10, 13-15, 19, and 33-36 stand rejected under 35 U.S.C. § 102(e) as being anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 6,210,717, issued to Choi et al. Withdrawal of this grounds for rejection is respectfully requested for the following reasons.

Claim 33 is the independent claim from which Claims 2-4, 8-10, 13-15, 19, and 34-36 depend.

For the reasons noted above, because the cited reference fails to exactly describe the claimed invention, the reference is not anticipatory. Withdrawal of the rejection is respectfully requested.

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Furthermore, applicants submit that the cited reference fails to teach, suggest, provide any motivation to make, or otherwise render obvious the claimed invention. The Choi polymers do not include a pH-sensitive linkage that, at pH less than 6.5, cleaves and releases a membrane-disruptive hydrophobic component thereby affecting membrane disruption and drug delivery. The Choi polymers include an amide link that joins a hydrophobic block to a hydrophilic block. First, the amide link will not be cleaved at a pH less than 6.5, as recited in the claimed invention. Second, these polymers are not designed to cleave at the amide link to release the polymer blocks. For the Choi polymers, drug (gene) delivery does not involve cleavage of the amide link. In contrast, hydrolysis of the pH-sensitive linkage at a pH less than 6.5 in the claimed invention releases a membrane-disruptive hydrophobic component that disrupts the membrane thereby delivering the drug (when the conjugate of the invention further include a drug).

The cited reference fails to suggest the claimed invention because the cited reference fails to teach or suggest a pH-sensitive linkage. The cited reference provides for drug delivery without bond cleavage of any kind. The claimed invention provides for drug delivery by simple acid hydrolysis of a chemically labile linkage that is pH-sensitive in the environment of the endosome. One skilled in the art would not be motivated by the teaching of the Choi reference to modify the amide-linked diblock copolymer to arrive at the pH-sensitive linked conjugate of the claimed invention.

Because the cited reference fails to teach, suggest, provide any motivation to make, or otherwise render obvious the claimed invention, the claimed invention is nonobvious and patentable of the cited reference. Withdrawal of the rejection is respectfully requested.

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The Rejection of Claims 2-4, 8-10, 13-16, 19, and 33-35 Under 35 U.S.C. § 102(e)

Claims 2-4, 8-10, 13-16, 19, and 33-35 stand rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,939,453, issued to Heller et al. Withdrawal of this grounds for rejection is respectfully requested for the following reasons.

Claim 33 is the independent claim from which Claims 2-4, 8-10, 13-16, 19, 34, and 35 depend. As noted above, Claim 33 relates to a hydrophilic conjugate having three components: (1) a hydrophobic component, which is membrane-disruptive and allows enhanced transport through a cellular membrane only when released from the hydrophilic conjugate, linked to (2) a hydrophilic component by (3) a pH-sensitive linkage that is stable at a pH between 6.8 and 8 and hydrolyzed at a pH less than 6.5 to release the hydrophobic component.

The Heller reference describes block copolymers that include hydrophobic and hydrophilic blocks. These polymers form micelles in aqueous solution making them suitable for capable for solubilizing hydrophobic materials, and form bioerodible matrices for the sustained release of active agents. The copolymers are polyethylene glycol (PEG)/poly(orthoester) (POE) block copolymers. The PEG blocks are hydrophilic and the POE blocks are hydrophobic.

In contrast to the claimed invention, the block copolymers described in the Heller reference do not include a hydrophobic component linked to a hydrophilic component by a Ph-sensitive linkage. More particularly, the block copolymers described in the reference do not include a hydrophobic component that is released from the hydrophilic conjugate by cleavage of the pH-sensitive linkage. The block copolymers described by the reference are, however, bioerodible or biodegradable. At Col. 5, lines 9-16, the reference states that bioerosion occurs by hydrolysis of linkages between and within the poly(orthoester) block. Thus, bioerosion (biodegradation) occurs through hydrolysis within the hydrophobic block and does not result in the release of a hydrophobic component (POE) that is membrane-disruptive and allows enhanced

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transport through a cellular membrane only when released from the hydrophilic component (PEG).

Because the cited reference fails to exactly describe the claimed invention, the reference is not anticipatory. Withdrawal of the rejection is respectfully requested.

The Rejection of Claims 2-4, 8-10, 13-16, 19, and 33-35 Under 35 U.S.C. § 102(e)/103(a)

Claims 2-4, 8-10, 13-16, 19, and 33-35 stand rejected under 35 U.S.C. § 102(e) as being anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,939,453, issued to Heller et al. Withdrawal of this grounds for rejection is respectfully requested for the following reasons.

Claim 33 is the independent claim from which Claims 2-4, 8-10, 13-16, 19, 34, and 35 depend.

For the reasons noted above, because the cited reference fails to exactly describe the claimed invention, the reference is not anticipatory. Withdrawal of the rejection is respectfully requested.

Furthermore, applicants submit that the cited reference fails to teach, suggest, provide any motivation to make, or otherwise render obvious the claimed invention. The Heller polymers do not include a pH-sensitive linkage that, at pH less than 6.5, cleaves and releases a membrane-disruptive hydrophobic component thereby affecting membrane disruption and drug delivery. First, although the Heller polymers are bioerodible and biodegradable, the bioerosion or biodegradation results from hydrolysis of linkages between and within the poly(orthoester) block. This bioerosion and biodegradation occurs through hydrolysis within the hydrophobic block and does not result in the release of a hydrophobic component (POE) that is membrane-disruptive and allows enhanced transport through a cellular membrane only when released from the hydrophilic component (PEG). Second, these polymers are not designed to cleave to release

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the polymer blocks, and more particularly, not to release a hydrophobic component that is membrane disruptive to effect drug delivery. In contrast, hydrolysis of the pH-sensitive linkage at a pH less than 6.5 in the claimed invention releases a membrane-disruptive hydrophobic component that disrupts the membrane thereby delivering the drug (when the conjugate of the invention further include a drug).

The cited reference fails to suggest the claimed invention because the cited reference fails to teach or suggest a pH-sensitive linkage that, when cleaved, releases a membrane-disruptive hydrophobic component that disrupts the membrane thereby delivering the drug. One skilled in the art would not be motivated by the teaching of the Heller reference to modify the PEG-POE block copolymer to arrive at the conjugate of the invention having a hydrophilic component (that is membrane disruptive when cleaved from the conjugate) linked to a hydrophilic component by pH-sensitive linkage that is hydrolyzed at a pH less than 6.5.

Because the cited reference fails to teach, suggest, provide any motivation to make, or otherwise render obvious the claimed invention, the claimed invention is nonobvious and patentable of the cited reference. Withdrawal of the rejection is respectfully requested.

The Rejection of Claims 2-4, 6, 8, 13, 16, 17, and 19

Under 35 U.S.C. § 112 Second Paragraph

Claims 2-4, 6, 8, 13, 16, 17, and 19 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The suggestions made by the Examiner are noted with appreciation. Claims 2-4, 6, 8, 17, 19, and 34 have been amended to recite proper Markush language. Applicants believe that Claims 13 and 16 are in proper form. Withdrawal of this grounds for rejection is respectfully requested.

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New Claims 38-44

Claims 38-44 have been added. Claims 38 and 41 are independent claims directed to a conjugate and composition that includes the conjugate, respectively. Claims 38-44 have been added to clarify the nature of the invention recited in Claim 33. Claims 38-44 are supported by the specification as originally filed.

Like Claim 33, Claim 38 recites a conjugate having three components. The three components recited in Claim 38 are (1) a hydrophobic synthetic vinyl-type polymer that is endosomal membrane-disruptive when released from the conjugate, (2) a plurality of pendant hydrophilic polyalkylene oxide components, and (3) a plurality of pH-sensitive linkages. Each of the pendant polyalkylene oxide components is covalently linked to the polymer through a pH-sensitive linkage that is stable at a pH between 6.8 and 8 and hydrolyzed at a pH less than 6.5. Claims 39 and 40 depend from Claim 38 and relate to the polymer and pH-sensitive linkage.

Claim 41 recites a composition that includes the conjugate of Claim 38 and a therapeutic or diagnostic agent. Claims 42-44 depend from Claim 41 and relate to the polymer, the pH-sensitive linkage, and the therapeutic or diagnostic agent, respectively.

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Conclusion

In view of the above amendments and foregoing remarks, applicants believe that Claims 2-4, 8, 9, 13-17, 19, 33-36, and 38-44 are in condition for allowance. If any issues remain that may be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicants' attorney at 206.695.1755.

Respectfully submitted,

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